

# Case Report Rapport de cas

## Caudal vena caval thrombosis following treatment of deep digital sepsis

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**Abstract** — A diagnosis of caudal vena caval thrombosis was made by ultrasonography of a Holstein cow presented for lethargy and poor milk production. Medical treatment was unsuccessful and the cow was euthanized. The diagnosis was confirmed at necropsy and *Fusobacterium necrophorum* was isolated from the thrombus. This paper discusses potential novel sources of caval thrombosis in this case.

**Résumé** — **Thrombose de la veine cave inférieure après le traitement d'une septicémie digitale profonde.**

Un diagnostic de thrombose de la veine cave inférieure a été posé par ultrasonographie pour une vache Holstein présentée pour de l'abattement et une faible production laitière. Le traitement médical a échoué et la vache a été euthanasiée. Le diagnostic a été confirmé à la nécropsie et *Fusobacterium necrophorum* a été isolé du thrombus. Cet article discute les nouvelles sources potentielles de thrombose de la veine cave dans ce cas.

(Traduit par Isabelle Vallières)

Can Vet J 2012;53:182–186

**C**audal vena caval thrombosis (CVCT) in cattle is most commonly caused by liver abscesses that erode into the caudal vena cava (CVC) resulting in a thrombus; however, other diseases with inflammatory foci can also result in a caval thrombus (1,2). The following case is unusual in that an initiating nidus of infection such as liver abscess, metritis, or mastitis was not identified. This paper discusses several possible sources of *Fusobacterium necrophorum* infection with secondary venal caval thrombosis in a Holstein cow, including a previous episode of deep digital sepsis treated with multiple regional intravenous perfusions. The disease pathogenesis may have been complicated by pregnancy and parturition.

### Case description

A 4 1/2-year-old Holstein Friesian cow was presented to the Oklahoma State University Boren Veterinary Medical Teaching Hospital (OSU-BVMTH) with a 3-week history of weight loss, hyporexia, and poor milk production following delivery of her second calf 1 mo earlier. No evidence of periparturient

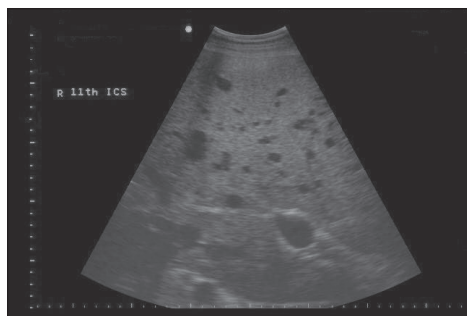
diseases, including mastitis, metritis, retained fetal membranes, ketosis, or hypocalcemia, had been present according to the herd manager and the herd veterinarian. During the 24 h prior to presentation the cow had appeared weak and was frequently in sternal recumbency.

One year prior to presentation the cow had been treated for a necrotizing sole ulcer of the right rear lateral claw. At that time the septic process extended deeply into the third phalanx and ultimately to the distal interphalangeal joint. Conservative medical and surgical treatment (antibiotics, debridement, bandaging, and placement of a wooden block on the right rear medial claw) was unsuccessful and digit amputation was performed at OSU-BVMTH. The right rear lateral claw was aseptically prepared prior to amputation with sterile obstetrical wire immediately distal to the level of the proximal interdigital cruciate ligament on the proximal phalanx (P1). Following amputation a sterile pressure bandage was applied to the amputation site, and the sterile bandage was replaced every 2 to 7 d until healthy granulation tissue covered the remaining portion of P1. Culture of the distal interphalangeal joint (DIPJ) synovial fluid yielded *Enterococcus faecalis* and a *Bacillus* species. Antibiotic sensitivity tests showed that the *E. faecalis* was susceptible only to ampicillin, enrofloxacin, penicillin, and trimethoprim-sulfonamide. After surgery, lameness worsened and osteomyelitis developed in the remaining portion of the proximal phalanx but resolved after 4 wk of intermittent treatment with debridement, flunixin meglumine (Banamine; Schering-Plough Animal Health, Union, New Jersey, USA), parenteral procaine penicillin G (Agricillin; AgriLabs, St. Joseph, Missouri, USA) and ceftiofur HCl (Excenel; Pfizer Animal Health, New York, New York, USA), and multiple regional intravenous perfusions (RIVPs) of ceftiofur sodium (Naxcel; Pfizer Animal Health). On her final recheck visit for the digital disease, no lameness, swelling, warmth, or discharge from the amputation site was present and

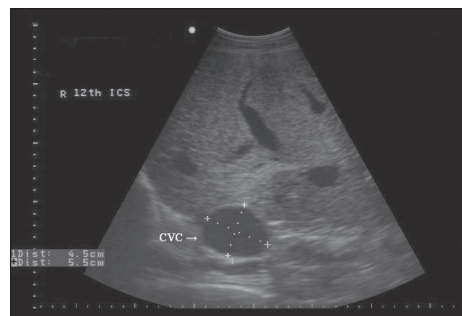
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**Figure 1.** Longitudinal ultrasonographic image of the liver in the dorsal 1/3 of the right 11th intercostal space, depicting the increased hepatic vasculature in a case of caudal vena caval thrombosis.



**Figure 2.** Longitudinal ultrasonographic image of the caudal vena cava and the liver in the dorsal 1/3 of the 12th intercostal space, showing the diameter of the caudal vena cava (4.5 cm × 5.5 cm) in a case of caudal vena caval thrombosis.

the region was completely covered by healthy granulation tissue. Eight months later, she was again presented to OSU-BVMTH.

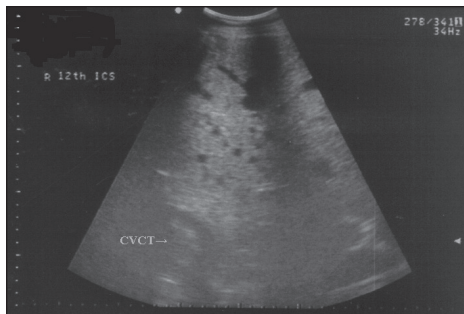
On initial physical examination the cow had a body condition score of 1.5/5, was mildly depressed, and stood with an arched back and extended head and neck. Muscle fasciculations were apparent in all 4 limbs. The cow was afebrile (rectal temperature: 37.2°C), tachycardic (heart rate: 120 beats/min), and hyperpneic (respiratory rate: 36 breaths/min) with an obvious abdominal component and a notable pause prior to expiration. Thoracic auscultation was within normal limits. Mucous membranes were moderately pale and tacky with a capillary refill time of > 2 seconds. The cow's eyes were sunken and dehydration was estimated at 7%. Abdominal contour was within normal limits for the generally poor body condition, ruminal motility was absent, and no pings were auscultated on abdominal percussion. The xiphoid pole test and withers pinch test both indicated cranial abdominal or caudal thoracic pain. Rectal examination was unremarkable. Bruxism was observed intermittently. As these clinical findings were nonspecific, additional diagnostics were performed.

Diagnostic tests included a complete blood (cell) count (CBC), serum chemistry panel, urinalysis, and fecal occult blood test (Hemoccult Fecal Occult Blood Test; Beckman Coulter, Fullerton, California, USA). Abnormalities in the CBC included a mild nonregenerative anemia [red blood cells  $5.4 \times 10^6/\mu\text{L}$ , reference range (RR): 5.5 to  $10.0 \times 10^6/\mu\text{L}$ ; hematocrit 23%, RR: 30% to 46%] and a leukocytosis (white blood cells  $18.0 \times 10^3/\mu\text{L}$ , RR: 4.0 to  $11.0 \times 10^3/\mu\text{L}$ ) characterized by a mature neutrophilia (14 220/ $\mu\text{L}$ , RR: 1000 to 4500/ $\mu\text{L}$ ). Hyperfibrinogenemia was present (20.6  $\mu\text{mol/L}$ , RR: 5.9 to 14.7  $\mu\text{mol/L}$ ). Pertinent serum chemistry findings included increased gamma-glutamyl transaminase (GGT) (302 IU/L, RR: 2 to 40 IU/L), increased aspartate aminotransferase (AST) (267 IU/L, RR: 60 to 132 IU/L), increased lactate dehydrogenase (LDH) (6180 IU/L, RR: 310 to 750 IU/L), hyperbilirubinemia (bilirubin 18.8  $\mu\text{mol/L}$ , RR: 0.0 to 13.7  $\mu\text{mol/L}$ ), hyperproteinemia (protein 93 g/L, RR: 55 to 79 g/L) characterized by hyperglobulinemia (globulin 7.2 g/L, RR: 22 to 46 g/L) and hypoalbuminemia (albumin 21 g/L, RR: 28 to 38 g/L). The cow was also hyperglycemic (7.8 mmol/L, RR: 2.8 to 5.0 mmol/L). Urinalysis results were within normal limits and the fecal occult blood test was negative. The clinicopathologic

findings were suggestive of a chronic inflammatory process involving the liver.

Hepatic ultrasound revealed marked venous congestion particularly in the region of the right 10th and 11th intercostal space (ICS), where the collateral hepatic vasculature was very prominent (Figure 1). The right hepatic vein was visualized within the 10th ICS and was distended, measuring 3.4 cm in diameter. The CVC was readily apparent in the 12th ICS. The vessel was markedly dilated, rounded, and measured 4.5 cm × 5.5 cm in diameter [RR: 1.8 to 5 cm (3)] (Figure 2). A distinct hyperechoic region within the CVC was visible and indicative of a thrombus (Figure 3). There was no evidence of ascites. Thoracic ultrasound showed no pleural defects or effusion, or evidence of endocarditis. Based on ultrasonographic examination CVCT was diagnosed. The owner was consulted and opted for treatment despite a poor prognosis.

A blood sample was collected aseptically from the right jugular vein and submitted for aerobic and anaerobic culture. Antimicrobial therapy had not been administered following resolution of the digital disease. Treatment was initiated with ceftiofur HCl (Excenel; Pfizer Animal Health), 2.2 mg/kg body weight (BW), SQ, q24h, flunixin meglumine (Banamine; Schering-Plough Animal Health), 1.1 mg/kg BW, IV, q24h, and morphine sulfate (Baxter Health Corporation, Deerfield, Illinois, USA), 0.2 mg/kg BW, IM, q6h. Antithrombotic therapy was considered but aspirin has not been shown to inhibit platelet function in Bovidae (4). Hourly monitoring for dyspnea, cyanosis, hemoptysis, and epistaxis was instituted. Appetite improved dramatically within 24 h of treatment. The patient remained afebrile and persistently tachycardic. Muscle fasciculations continued. On the 4th day of hospitalization hepatic ultrasound showed no changes from previous findings. On the 6th day, a blood clot was noted in the right nares. Five hours later the patient became recumbent, acutely dyspneic, and began open-mouth breathing and groaning on expiration. Thoracic auscultation was suggestive of pulmonary edema. Furosemide (Furoject; Butler Animal Health, Dublin, Ohio, USA) was administered (2 mg/kg BW, IV) along with morphine sulfate (0.2 mg/kg BW, IM) but clinical signs persisted. The cow was euthanized with pentobarbital and submitted for complete postmortem examination. Blood culture revealed *Fusobacterium necrophorum* and a *Bacillus* species.



**Figure 3.** Longitudinal ultrasonographic image of the liver immediately dorsal to the costochondral junction in the right 12th intercostal space, depicting the thrombus within the caudal vena cava.

On gross examination, the CVC was distended and variably occluded by an approximately 20-cm long, 6-cm diameter, yellow and red dense thrombus that extended from the level of the diaphragm to the juncture with the hepatic vein (Figure 4). The luminal surface of the vena cava along the length of the thrombus was thickened, irregular, and coated with a thick layer of fibrin.

The liver was diffusely friable with an enhanced reticular pattern. Scattered throughout the hepatic parenchyma were dozens of 0.5 to 1 cm diameter, pale grey areas. The gallbladder wall, abomasal folds, and mesojejunum were markedly edematous.

There was no gross evidence of active inflammation at the site of digital amputation. The surgery site was well-healed.

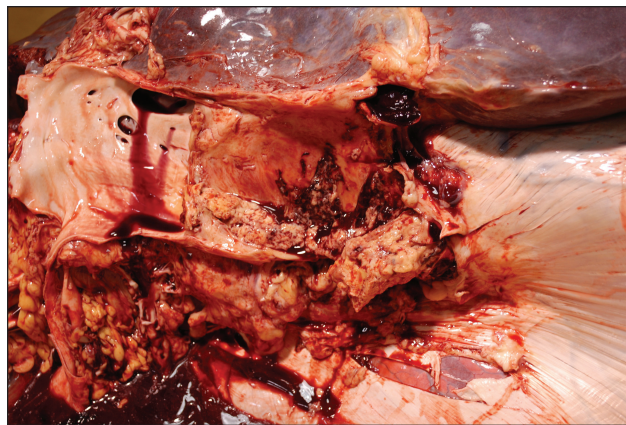
Representative tissue sections were collected and placed in 10% neutral-buffered formalin. The fixed samples were routinely sectioned, paraffin-embedded, and stained with hematoxylin and eosin.

Histologically, the endothelial surface and tunica intima of the CVC were obliterated by aggregates of necrotic cellular debris admixed with inflammatory cells and fibrin. Fewer inflammatory cells infiltrated deep into the underlying tunica media. Numerous reactive fibroblasts and small vessels with reactive endothelium were scattered throughout the media and the adjacent adventitia. There were scattered foci of mineralization and hemorrhage within the tunica media.

Within the liver, the centrilobular sinusoids were severely congested and hepatocytes within zones 2 and 3 were shrunken, degenerate, and necrotic — consistent with hypoxia. Regionally extensive areas of fibrosis with marked bile duct hyperplasia which obliterated the adjacent hepatocellular architecture were randomly scattered throughout the section. This change was consistent with chronic hypoxia and hepatocellular necrosis with fibrosis.

Within the lung, multifocal large arteries were occluded with large lakes of necrotic cellular debris, fibrin, and degenerate neutrophils. There was extensive coagulative necrosis of the surrounding alveolar architecture. In less affected areas, the tunica intima of large arteries was markedly, multifocally thickened.

Bacteriologic culture of the caval thrombus yielded *F. necrophorum*, *Eubacterium lentum*, *Pseudomonas aeruginosa*, and *Escherichia coli*. Unfortunately, bacterial isolates were not saved and strain typing (pulsed field gel electrophoresis, restric-



**Figure 4.** Intravenous thrombus in the caudal vena cava in-situ, approximately 20-cm long and 6-cm in diameter, extending from the level of the diaphragm to the juncture with the hepatic vein.

tion fragment length polymorphism) could not be performed on either the *Fusobacterium necrophorum* isolated from the systemic circulation and the thrombus, or the *Bacillus* species isolated from the DIPJ synovial fluid culture and the systemic circulation. Lack of isolates precluded identification of the *Bacillus* species.

## Discussion

Caudal vena caval thrombosis in cattle is most commonly caused by liver abscesses and typically occurs within the hepatic portion of the vena cava, resulting in partial or complete occlusion of the vessel (1). Diseases with inflammatory foci such as thrombophlebitis, metritis, or mastitis can also result in a caval thrombus (1,2). Emboli from the thrombus may spread to other organs resulting in endocarditis, embolic pneumonia, hepatic and renal abscessation, or erosion of pulmonary vessels causing intrapulmonary or intrabronchial hemorrhage that can terminate in sudden death (1).

Clinical signs of CVCT may be vague or suggestive of bronchopneumonia, and include thin body condition, chronic weight loss, decreased appetite, fever, tachypnea, abnormal lung sounds, and coughing (1,5). Antemortem diagnosis of CVCT can be challenging. Caudal vena caval thrombosis may be suggested by hematological and serum biochemical testing but CVC ultrasonography revealing dilatation and a rounded appearance of the normally triangular vessel is suggestive of CVCT (1,5). Definitive ultrasonographic diagnosis is possible if the thrombus can be visualized within the lumen of the CVC, but this is rare (1,2,6). Sigrist et al (2) described diagnosis of CVCT in 2 cows via intraoperative ultrasound examination of the liver, offering an additional route for antemortem identification of affected animals. Treatment is typically not recommended due to the poor prognosis, although successful treatment has been reported (1,2).

The underlying cause of the CVCT in this case is unknown as an initiating inflammatory nidus such as liver abscess, metritis, or mastitis was not identified and most animals treated for septic digital processes do not develop CVCT. We postulate that the previous episode of DDS treated with multiple RIVPs may

have led to the development of CVCT. The disease pathogenesis could have been complicated by pregnancy and parturition.

Antemortem diagnosis via transabdominal ultrasound is rarely possible because the thrombus is situated cranial to the linea phrenicocostalis and is obscured by the lungs (1). Immediate noninvasive confirmation of CVCT allowed us to pursue diagnostics not previously described in the veterinary literature. This is the first reported case in which blood culture was used in an attempt to guide antibiotic therapy in the treatment of CVCT.

Culture of *F. necrophorum* and *Bacillus* from the blood and *F. necrophorum* from the thrombus raises interesting questions regarding the pathophysiology underlying CVCT in this patient. *Fusobacterium necrophorum* and *Arcanobacterium pyogenes* are the agents most commonly associated with CVCT (7). They are also the agents most commonly cultured from hepatic abscesses in cattle without CVCT (8–10), suggesting that underlying liver disease is the ultimate cause of the thrombi. No hepatic abscess was found, and centrilobular hepatic degeneration and necrosis in this case is attributed to altered tissue perfusion secondary to caval thrombosis. These findings suggest that the liver was not the origin of the thrombus. Both bacterial species isolated by blood culture, however, are commonly associated with pathologic lesions of the bovine foot. *Fusobacterium necrophorum* can act synergistically with *Bacillus* spp. to cause a variety of pedal infections (11,12).

The cow described in this report was seen over a dozen times in the clinic for DDS unresponsive to conventional therapy. Six of these visits involved RIVP of the distal limb with either ceftiofur sodium or 2% lidocaine for regional analgesia prior to debridement of osteolytic lesions. Prior to RIVP the skin overlying the right dorsal common digital vein was clipped, scrubbed with chlorhexidine and saline, and rinsed with alcohol. Surgical preparation was not performed, allowing for speculation as to whether repeated intravenous access in an anatomic location known to harbor pathogenic bacteria could have ultimately resulted in CVCT.

In human medicine the association between *F. necrophorum* and septic venous thrombosis is well-documented and classically presents as Lemierre's syndrome, in which a primary cephalic infection results in thrombosis of the internal jugular vein and subsequent disseminated abscess formation (13). Thrombosis in these cases has been attributed to the aggregation of platelets, believed to be mediated by virulence factors of *F. necrophorum* (14–16). Variants of Lemierre's syndrome have been recognized in which *Fusobacterium* species resulted in portal vein or femoral vein thrombosis (17,18).

Regional intravenous perfusion of antibiotics or local anesthetics into the distal limb is often used to treat bovine digital disorders. Studies on RIVP in the bovine using cefazolin, ceftiofur sodium, and florfenicol have shown that antimicrobial levels in venous blood and synovial fluid in joints distal to the tourniquet can reach concentrations above the minimal inhibitory concentration (MIC) for common bacterial pathogens associated with deep digital sepsis (DDS) (19–21). Complications associated with RIVP have included phlebitis and venous thrombosis distal to the tourniquet (21–24). One description of 2 cows that developed generalized distal limb venous thrombosis credited

the condition to multiple factors including endotoxemia from preexisting infection, RIVP, and tourniquet placement which can result in local ischemia, acidosis, and hypoxia (23,25,26). The conclusion reached by the authors was that RIVP with antibiotics should not be performed more than once if digital sepsis is present (23).

Perhaps the most concerning complication reported in foals has been the association of RIVP used to treat septic processes in the tibiotarsal joints with the development of secondary septic foci (27). Clinical signs consistent with septicemia following intravascular perfusion of the limb have also been documented in humans (28). In 1 report, 4 out of 15 patients undergoing treatment for osteomyelitis developed signs of systemic sepsis within 4 h following RIVP, and 1 patient was blood-culture positive, resulting in a recommendation that patients receive systemic antibiotics prior to institution of such therapy (28). Septic phlebitis, thrombophlebitis, or septicemia from repeated RIVP treatments could have been the underlying cause of CVCT in this cow. Unfortunately the digital veins from the affected limb in our cow were not scrutinized histologically and this hypothesis was not confirmed or denied by necropsy.

Alternative sources for the original nidus of infection resulting in CVCT could be direct inoculation via portal venous blood, previous metritis, or retained fetal membranes, subclinical or clinical mastitis, the initial septic digital lesions, or postoperative osteomyelitis of the proximal phalanx. The culture of a *Bacillus* spp. from both the DIPJ synovial fluid and the systemic circulation would seem to support one of the latter hypotheses, although 359 days elapsed between the 2 cultures. There was no history of postparturient diseases. Although milk somatic cell counts and cultures were not available, no gross or histologic evidence of mastitis or metritis was observed at necropsy.

Most reports of Lemierre's syndrome describe a comparatively short period of time between the initiating event and venous thrombosis (29). No other illnesses had been apparent in this cow although she had recently calved. It seems possible that her gravid state may have influenced the disease course via several mechanisms including increased intra-abdominal pressure (IAP) and hypercoagulability. Human medical literature has long recognized that patients with increased IAP may have focal narrowing of the upper abdominal inferior vena cava (IVC) either at or just below the level of the diaphragm (30–32). Pregnancy in women has been associated with increased IAP (33) and cattle experience a large increase in IAP during parturition (34). Increased IAP may have resulted in narrowing of the intrahepatic portion of the CVC creating a site of turbulent blood flow that predisposed this cow to thrombus development.

Normal human pregnancies are accompanied by a hypercoagulable state believed to have evolved as a protective mechanism against hemorrhage during parturition or miscarriage (35). The outcome of a study on the blood coagulation profile in pregnant ewes likewise suggested that prepartum hormonal changes could result in hypercoagulability during parturition (36). The cow herein was pregnant when the diagnosis of DDS was made. It is possible that a state of hypercoagulability may have resulted in a predisposition to thrombosis of either the distal limb veins or the CVC. Endotoxemia from a gram-negative bacteremia could

have additionally overwhelmed the endothelial antithrombotic abilities leading to vascular endothelial damage and activating the clotting cascade culminating in hemostatic dysfunction or coagulopathy (23,37,38).

In summary, this is the first report to describe CVCT following treatment of DDS with repeated RIVP of antibiotics or local anesthetics. The etiopathogenesis of CVCT in this case may have been complicated by the cow's gravid condition while undergoing treatment of a septic digital disorder. Blood culture has not been previously reported as an ancillary diagnostic in CVCT but can be used when determining a course of therapy. Surgical preparation of the dorsal common digital vein may be indicated if RIVP is used repetitively in the treatment of septic conditions of the distal limb because of the potential for introduction of commensal organisms into the systemic circulation. CVJ

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